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New Analytical Method Development and Validation for Simultaneous Estimation of Domperidone and Cinnarizine in Bulk by RP-HPLC

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ABSTRACT

The study's objective is to provide a rapid, simple, accurate, and cost-effective RP-HPLC assay technique for the simultaneous quantification of domperidone and cinnarizine in pharmaceutical bulk. Domperidone and cinnarizine in bulk have been successfully separated using this approach. Separation was carried out at 226 nm on a C18 SunfireTM (5 m, 250 mm 4.6 mm) analytical column using an Orthophosphoric acid and acetonitrile (60:40) mobile phase operating in isocratic elution mode at a flow rate of 1.0 ml/min. Domperidone had a retention time of 2.52 minutes, whereas Cinnarizine's was 5.18 minutes. PDA detection at 226 nm based on peak area with linear calibration curve in concentration ranges of 0-5 g/ml (0.9999) and 0-25 g/ml (0.9996) allowed for accurate quantitation of Domperidone and Cinnarizine, respectively. Domperidone and cinnarizine

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had LODs of 0.3325 and 0.615 g/ml, respectively. The suggested approach is well-suited for use in quality-control labs for bulk quantitative analysis of the medications, both alone and in combination, since it is straightforward and quick while maintaining high accuracy and precision.

Keywords: Domperidone, Cinnarizine and RP-HPLC.

Introduction:

Piperazine derivative cinnarizine (CIN) (Fig. No. 01) blocks calcium channels, dopamine D2 receptors, and histamine H1 receptors [1,2]. It is beneficial for vestibular symptoms of diverse causes [2,3], not only vertigo/Meniere's disease, nausea, vomiting, and motion sickness. By blocking voltage-gated calcium channels, CIN reduces the contractions of vascular smooth muscle cells [3]. By binding to dopamine D2 receptors, histamine H1 receptors, and muscarinic acetylcholine receptors, CIN may reduce vomiting caused by motion sickness [4, 5]. The vestibular system in the inner ear sends signals to the vomiting centre in the hypothalamus, and this medication blocks those signals [4,5].

Domperidone (DOM) (Fig. No. 02) is an antiemetic and gastric prokinetic medication used to treat motility problems [6,7]. DOM works by blocking the activity of dopamine receptors. As an antiemetic, it is often used to mitigate the ill effects of Parkinson's drugs and cancer treatments that may trigger nausea and vomiting. DOM's antiemetic properties are linked to its ability to inhibit dopamine receptors in the stomach and the chemoreceptor trigger zone.

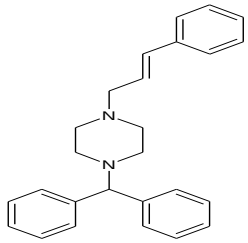

Fig.No. 01 : Structure of cinnarizine

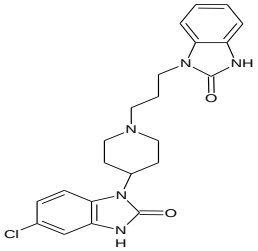

Fig.No. 02 : Structure of Domperidone

A review of the relevant literature indicates that only a handful of techniques have been published for the estimation of these medications in bulk and combination dose forms, such as the simultaneous estimate of domperidone [8-10] and cinnarizine [11-15] in tablet dosage form by RP-HPLC. However, the selectivity and sensitivity of these chromatographic approaches is subpar. The current study aimed to provide a straightforward, quick, precise, and accurate RP-HPLC assay technique for the quantification of both domperidone and cinnarizine simultaneously. The suggested approach may be effectively used for quality assurance.

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MATERIALS AND METHODS

Drug substance

Domperidone and Cinnarizine, Orthophosporic acid (HPLC grade) and acetonitrile (HPLC grade), HPLC system (Shimadzu SPD-20A, Tokyo, Japan).

Instrumentation

All HPLC experiments were carried out on anHPLC system (Shimadzu SPD-20A, Tokyo, Japan) separation module, with a photodiode array detector in isocratic mode using an Autosampler. Data collection and processing were done using lab solution software. The analytical column used fortheseparationwas C18 SunfireTM (5 µm, 250 mm × 4.6 mm) andthe other equipment used was a pHmeter (Eutech), Weighingbalance (Shimadzu) and Ultrasonicator (Unichrome, UCA701).

Reagents required

Acetonitrile (HPLC grade), Water (HPLC grade)and Ortho phosphoric acid.

Preparation of solutions

Diluent: The mobile phase as such used as diluent throughout the procedure.

Preparation of orthophosphoric acid buffer solution:

Dissolved 1 milliliter of orthophosphoric acid in 1 liter of HPLC-grade water and filtered 0.45-micron nylon filter.

Preparation of mobile phase:

The mobile phase was made by combining a orthophosphoric acid buffer f and acetonitrile at a 60:40 ratio and filtered via a 0.45-micron membrane filter.

ortho phosphoric acid buffer solution preparation:

Mixed 1ml of ortho phosphoric acid and dissolved in 1lter of HPLC grade water. Which was then filtered through 0.45µ nylon filter.

Preparation of mobile phase

Mobile phase was prepared by mixing ortho phosphoric acid buffer and acetonitrile taken in the ratio 60:40 and was filtered through 0.45µ membrane.

Preparation of standard stock solution

Weighed 1.85mg of domperidone and 2.46mg of cinnarizine into a 10ml volumetric flask using a digital microbalance. The aforementioned solution was added to 7 ml of diluent, sonicated to dissolve it, and then diluted to volume using diluent, and finally diluted to a final volume of 1 ml by adding more diluent..

Chromatographic conditions

High Performance Liquid Chromatography equipped with PDA detector.

For Domperidone and Cinnarizine (isocratic)

Column	:	C18 SunfireTM (5 µm, 250 mm × 4.6 mm)
Wavelength	:	226 nm
Injection Volume	:	10µl

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Column Temperature : Ambient

Flow rate : 1.0 ml/min

At 2.52 minutes, the DOM peak was found to have an area of 187,273, with a tailing factor of 1.40. As shown in Fig. 3 and Table 1, the CIN peak was seen at 5.18 min with a peak area of 2748064, a tailing factor of 1.37, and a resolution of 10.25. This experiment was deemed optimal due to its positive outcomes and shorter retention duration. DOM has a retention time of around 2.52 minutes. CIN has a retention time of 5.18 minutes, roughly.

Table 1: System suitability parameters

S.No.	Name of the Peak	Retention Time (Mins)	Peak Area	Tailing Factor	Resolution	Plate Count
01	Domperidone	2.52	1872735	1.40	---	4200
02	Cinnarizine	5.18	2748064	1.37	10.25	5245

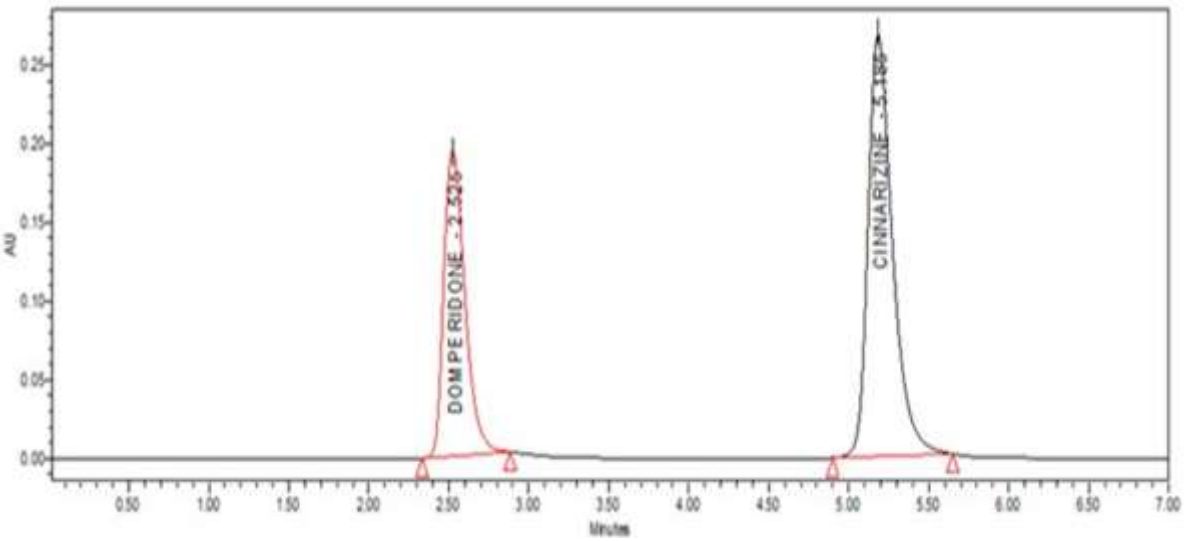

Fig.No. 03 : Typical Chromatogram of Domperidone and Cinnarizine

Preparation of sample solution

About 10 mg of sample was weighed into a 10 ml volumetric flask, and then 7 ml of diluent was added. The mixture was then sonicated to dissolve the material, and then diluted to volume with diluent. Further diluted 1 ml to 10 ml with the diluent and filtered through 0.45µ Nylon syringe filter.

Procedure

10 µl of active DOM and CIN standard solutions were injected five times, chromatograms were recorded, and peak responses were assessed. The parameters of the system's appropriateness need to be measured. The amount of DOM and CIN in the sample was determined by analyzing the peak responses.

Method Validation

The following factors were investigated in order to validate the HPLC technique for the determination of DOM and CINaccording to the protocol and show that the method is suitable for its intended usage. All validation criteria were implemented in accordance with ICH standards.

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Linearity and Range

The concentrations of DOM and CIN that showed a linear relationship with peak area were (01 - 05 g/ml), (05 - 25 g/ml).Results are shown in (Fig.4 & 5), (Table 2 & 3), and the linearity of the calibration curve is confirmed by the high value of the correlation coefficient of the regression equation.

Table 2: Linearity data of DOM

S.No.	Concentration (µg/ml)	Peak Area
1	0	0
2	1	374548
3	2	749098
4	3	1144645
5	4	1508285
6	5	1872735
Slope		**376012**
Intercept		**1520.9**
Regression		**0.9999**

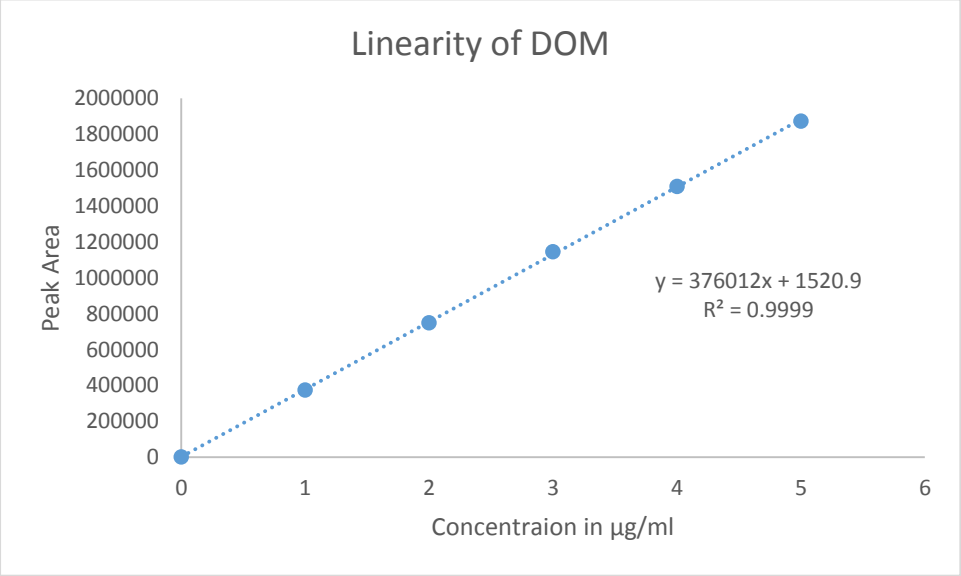

Fig.No. 04 : Linearity of Domperidone

Table 3: Linearity data of CIN

S.No.	Concentration (µg/ml)	Peak Area
1	0	0
2	5	549613
3	10	1099326
4	15	1698839
5	20	2208451
6	25	2748064

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Slope	**110379**
Intercept	**4309.8**
Regression	**0.9996**

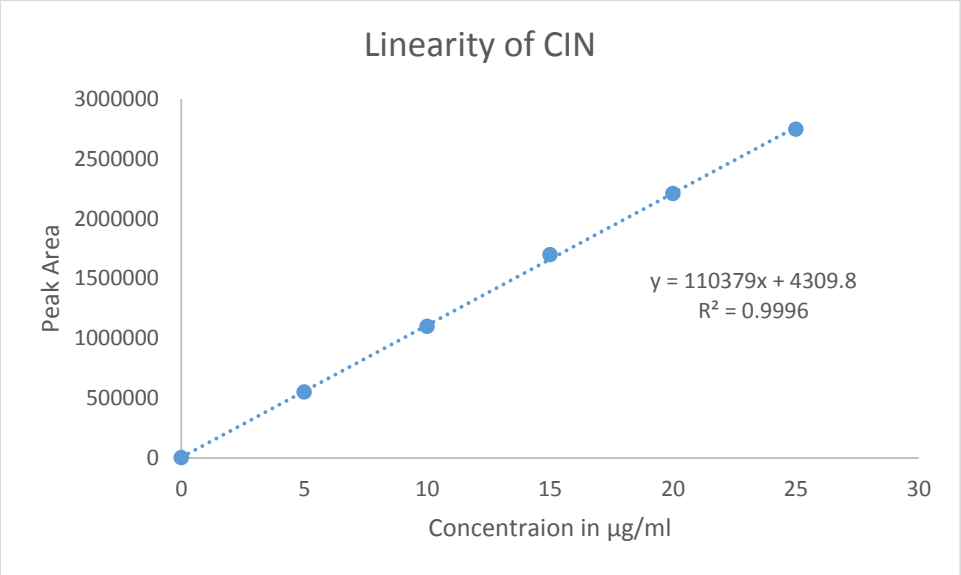

Fig.No. 04 : Linearity of Cinnarizine

Accuracy and Precision:

Accuracy as recovery was examined by spiking previously analyzed test solution with extra Standard drug at three different concentration levels. With a relative standard deviation (RSD) of less than 2%, we observed that the suggested technique is accurate for the simultaneous estimate of both DOM and CIN, with a recovery of 100.11 % for DOM and 100.35% for CIN, respectively. The high reproducibility and low RSD values show that the Method is reliable. (table-4).

Table 3: Precision data of DOM and CIN

Sample Preparation No.	**DOM Assay (%)**	**CIN Assay (%)**
1	100.49	100.58
2	100.12	100.22
3	99.93	99.89
4	98.43	100.02
5	100.03	100.15
6	101.66	101.26
Mean	**100.11**	**100.35**
SD	**1.04**	**0.5017**
RSD (%)	**1.04**	**0.500**

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Robustness:

Table no.4 displays the results of the robustness analysis. Both components maintained similar tailing factors, elution orders, resolutions, relative standard deviations, and recoveries. It was determined that the RSD of the peak locations was much lower than 2.0%.

Table 4: Robustness data of DOM and CIN

Condition	Domperidone			Cinnarizine		
	% RSD	Tailing Factor	%Recovery	% RSD	Tailing Factor	%Recovery
1) Change in Flow rate						
Normal Condition (1 ml per minute)	0.05	1.09	99.48	0.06	1.09	99.58
Flow rate (0.8ml per minute)	0.06	1.08	99.17	0.07	1.08	99.25
Flow rate (1.2 ml per minute)	0.09	1.08	98.38	0.08	1.08	98.21
2) Change in minor component in the mobile phase						
Normal Condition (Buffer: Acetonitrile) (60 : 40))	0.05	1.08	99.59	0.08	1.08	99.89
(Buffer: Acetonitrile) (62 : 38)	0.18	1.08	99.43	0.45	1.11	99.41
(Buffer: Acetonitrile) (58 : 42))	0.09	1.06	101.57	0.42	1.12	101.21
3) Change in Wave Length						
Normal:Wave Length 226 nm	0.04	1.09	99.89	0.45	1.11	99.92
Wave Length 221 nm	0.09	1.05	98.97	0.12	1.12	98.88
Wave Length 231 nm	0.08	1.07	98.83	0.18	1.07	100.12

Ruggudness:

Domperidone and Cinnarizine had respective mean peak areas of 1,87,284 and 2,74,244, with an RSD of 0.35 and 0.28%, respectively.

SUMMARY

For the purpose of bulk estimation of DOM and CIN, an effort has been undertaken to create a novel validated RP-HPLC technique. Since the literature review showed that few approaches exist for bulk estimate of DOM and CIN, there is a pressing need for a straightforward, cost-effective, and accurate approach to this problem.

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DOM and CIN concentrations were estimated by injecting and eluting Buffer and Acetonitrile (60:40v/v) onto a C18 SunfireTM (5 m, 250 mm 4.6 mm) column at a flow rate of 1 ml/min, with an injection volume of 10 l. Retention durations of 2.52 and 5.18 min were observed for the DOM and CIN peaks, respectively.

Following its improvement, the procedure was verified in accordance with ICH standards for system compatibility, linearity, sensitivity parameters, precision, accuracy, and robustness. All validation parameters came back within acceptable ranges. RSD values for the assays were below 2. Recoveries were in the range of 98%-102%.

CONCLUSION

The suggested RP-HPLC technique required less time and effort to complete while still being simple, quick, accurate, precise, specific, robust, and cost-effective. Consequently, it is a preferred technique for the joint determination of domperidone and cinnarizine. The devised approach was fully validated according to ICH standards in all respects.

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